



Aldehyde allylation

in liquid carbon dioxide

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Summary

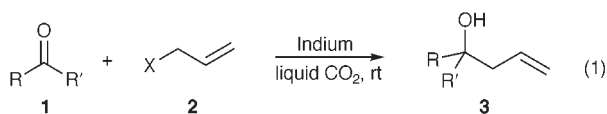
Various aldehydes react with allyl bromide mediated by indium in liquid carbon dioxide to give homoallylic alcohols.

Introduction

In recent years, owing to an increased awareness of the detrimental effects that organic solvents have on the environment, a substantial amount of research has been devoted to exploring chemistry that is more environmentally friendly.¹ A large part of this endeavor concerns itself with solvents. Almost all chemical processes make use of organic solvents at some point. These organic solvents, used in academic research and in industry, are often very harmful to the environment, and as a result are frequently subject to government restrictions and high waste disposal costs. Consequently, methods that successfully minimize their use are the focus of much attention. Among our efforts at finding alternative media for organic reactions, we explored the feasibility of conducting indium mediated allylation of aldehydes using liquid carbon dioxide as the solvent.

Results and discussion

We initially had considered attempting the allylation in supercritical CO₂. Despite an established history as an effective extractor, in recent years attention has been paid to the use of supercritical fluids as reaction mediums.² CO₂ in particular has emerged as a popular choice for a reaction solvent. It has proven an effective solvent for a number of reactions,³ including the Diels–Alder reaction,⁴ the Pauson–Khand reaction⁵ and free radical brominations.⁶ However, we quickly became intrigued with the idea of using liquid CO₂ instead. For one thing, the temperatures and pressures required for a liquid phase CO₂ system are mild enough that setting up such a system in the laboratory was quite easy. Various studies⁷ attest to the ability of liquid CO₂ to substitute effectively for supercritical CO₂ in different chemical processes. In our research, we found indium metal to be a highly effective mediator in coupling reactions between carbonyl compounds **1** and allyl bromide **2** in liquid carbon dioxide. The reaction went smoothly at room temperature, producing the cross-coupled product **3** exclusively [eqn. (1)].



The problem with which we were initially confronted was one of system design. The exigencies of working with a high pressure system imposed certain constraints on the reaction; instead of adding our reactants to the solvent, as is normal in organic chemistry, it was necessary for us to reverse this order. To begin the

reaction, we mixed together in the metal bomb the aldehyde, indium, and allyl bromide, and only then added liquid CO₂ to the system. It had recently been demonstrated by our group that indium promoted the same carbonyl allylation under neat conditions,⁸ and there was thus some concern that the allylation reaction would begin before we had even added the liquid CO₂. However, it had also been established in that study that vigorous stirring was necessary to promote the neat allylation, and this presented us with our window of opportunity. While the bomb was filling with liquid CO₂, the entire vessel was completely submerged in an ice-water bath, and this served a two-fold purpose. First, the lower temperature promoted condensation of gaseous CO₂, and second, it was hoped that the lower temperature would help impede any neat reaction of the mixture that might possibly occur. Stirring was started only once the vessel was filled with liquid CO₂.

For the inaugural reaction in this project, we mixed benzaldehyde, allyl bromide, and indium powder in a 10 mL high pressure metal bomb. Liquid CO₂ was added, and the system was stirred 48 h at room temperature. The reaction was worked up with diethyl ether and 1M HCl. After drying over magnesium sulfate

Green Context

In most reactions, the major component is the solvent. Care must therefore be taken to ensure that solvent is chosen to minimise waste generation, both through supporting efficient reaction and facilitating product isolation and solvent recovery. However, the recent increased awareness of the potentially detrimental effects of organic solvents on the environment has led to a rapid growth in research into alternative reaction media. In this respect, supercritical fluids, in particular carbon dioxide, have recently been shown to be excellent for many reactions (see *e.g.* *Green Chemistry*, 1999, 1, 65 and 261 (preceding paper)). Carrying out reactions in liquified gases under sub-critical conditions can be easier experimentally, and can often have similar benefits—the solvent often has similar properties to the supercritical equivalent, and is separated by depressurisation, ready to be used again. This article describes a clean carbon–carbon bond forming reaction mediated by indium which can be carried out efficiently in liquid carbon dioxide under mild conditions. It is hoped that this breakthrough will encourage more studies of the use of metallic reagents in supercritical carbon dioxide. An alternative procedure to similar products has been described in *Green Chemistry*, 1999, 1, 167.

DJM and JHC

and removing the solvent under vacuum, the ^1H NMR spectrum of the crude material indicated that the cross coupling product had been obtained cleanly, with very little unconverted benzaldehyde left over. No by-products were observed in the ^1H NMR spectrum of the crude reaction mixture. Subsequent purification of the crude product by flash chromatography afforded the desired product in 82% yield.

Various carbonyl compounds were then allylated in a similar manner (Table 1). For each aldehyde, the reaction proceeded smoothly, providing the resulting alcohol in moderate to good yield. Some of the aldehydes reacted more quickly than others; to ensure completion in each case, the mixtures were generally stirred for 48 hours. Aliphatic (entry 10) and aromatic aldehydes gave similar yields. For the most part, the presence of substituents on the benzene ring did not have an appreciable effect on the yield or rate of the reaction. In nearly all cases, conversions greater than 85% were obtained, in many cases being quantitative. The yields of the different products, however, belie the effectiveness of the reaction. The relatively lower isolated yields do not stem from a limitation on the reaction's part; rather they are the result of the inherently awkward workup (due to the reaction apparatus) in which some of the product is inevitably lost. In all cases, to avoid further neat reaction of the system after the CO_2 was vented, it was necessary to transfer as quickly as possible the reacted mixture to the receptacle where it was worked up. It was sometimes necessary to sacrifice a small amount of the product to facilitate this transfer, and this is reflected in the yields. Simple changes in the design of the liquid CO_2 reaction vessel should surmount these problems.

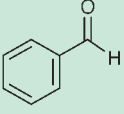
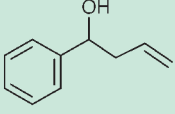
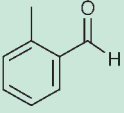
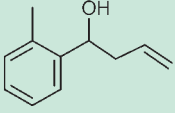
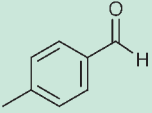
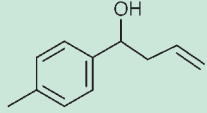
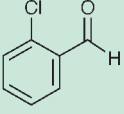
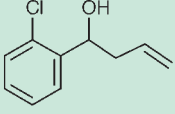
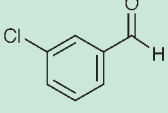
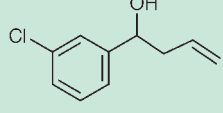
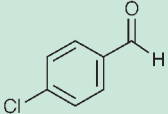
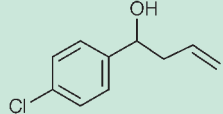
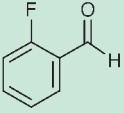
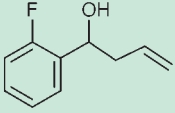
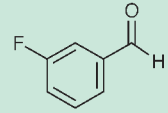
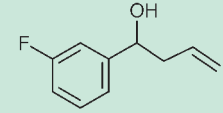
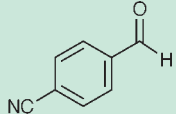
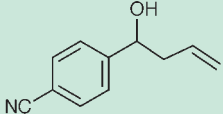
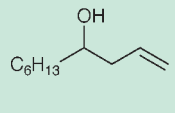
As previously indicated, there was initially some concern that the reaction was taking place while still neat, before the addition of the liquid CO_2 . To demonstrate to ourselves that the allylation reaction in liquid CO_2 was indeed occurring in liquid CO_2 , we needed to successfully allylate an aldehyde that had proven to be impossible to allylate under neat conditions. A salient limitation on the part of the neat reaction had been its inability to allylate solid aldehydes. Various attempts to perform such an allylation under neat conditions had not been successful. We chose the solid 4-cyanobenzaldehyde as our carbonyl (entry 9). The solid aldehyde was mixed with the reactants, and to the mixture was added a drop of Fomblin[®] (MW = 1800), a perfluoropolyether surfactant.⁹ Following the same procedure as for the other carbonyls, reaction of the mixture provided the corresponding alcohol in 58% yield. This effectively demonstrated that liquid CO_2 can facilitate reactions impossible under neat conditions.

In summary, the indium mediated-allylation of carbonyl compounds using liquid carbon dioxide as a solvent was shown to be quite effective in most cases. It presents a relatively clean and efficient method of forming homoallylic alcohols. Using liquid CO_2 as a solvent avoids the waste disposal problems associated with organic solvents. In contrast to the corresponding neat allylation, the liquid CO_2 mediated reaction was able to allylate solid aldehydes successfully.

Experimental

A typical experimental procedure: A mixture of benzaldehyde (219 mg, 2.06 mmol), allyl bromide (1.5 equiv., 380 mg, 3.09 mmol), and indium (1.5 equiv., 360 mg, 3.09 mmol) was placed in a 10 mL high pressure metal bomb. The bomb was then connected to a siphon cylinder containing liquid carbon dioxide, placed in an ice water bath, and filled to capacity over about one minute with liquid carbon dioxide at approximately 850 psi. The bomb was then removed from the ice water bath and the mixture

Table 1

Entry	Substrate	Product	Yield(%)
1			81.8
2			45.3
3			74.1
4			57.7
5			56.8
6			55.3
7			37.8
8			68.8
9			57.8
10	$\text{C}_6\text{H}_{13}\text{CHO}$		59.0

was stirred vigorously at room temperature for 48 h. After venting the carbon dioxide from the reaction vessel, the residue was quenched with diethyl ether (5 mL) and 1M HCl (3 mL). The mixture was extracted with ether (3×10 mL), and the combined ethereal extracts were washed with water and dried over magnesium sulfate. The solution was then filtered and concentrated under vacuum to produce the crude product, which was subsequently purified by column chromatography, giving the desired 1-phenylbut-3-en-1-ol (282 mg, 82%) as a colourless oil.

Caution: When working with liquid CO_2 , care should be taken to minimize the dangers that are associated with such high pressure systems. Among other precautions, a plexiglass shield may be used as protection from any possible explosions. Extra care should also be taken when venting the bomb; releasing the pres-

sure too quickly can result in the sudden expulsion of the system's contents.

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